

PATENT COOPERATION TREATY

Rec'd IFD

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

To:

HAMILTON, BROOK, SMITH
& REYNOLDS, P.C.
Attn. Sanders, Deirdre E.
530 Virginia Road
P.O. Box 9133
Concord, MA 01742-9133
UNITED STATES OF AMERICA

Date of mailing
(day/month/year)

22/04/2005

Applicant's or agent's file reference

3518.1024002

PAYMENT DUE

within **ONE MONTH** from
the above date of mailing

International application No.

PCT/US2004/039589

International filing date
(day/month/year)

23/11/2004

Applicant

DEPUY SPINE, INC.

1. This International Searching Authority

- (i) considers that there are 9 (number of) inventions claimed in the international application covered by the claims indicated ~~below~~ on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~below~~ on the extra sheet:

FOREIGN DOCKETING

ADE 12/11/2005

SRV 22/04/2005

ADE 22/04/2005

Completed By SDL

- (ii) ☒ has carried out a partial international search (see Annex) ☐ will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:

see annex

- (iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby **invited**, within the time limit indicated above, to pay the amount indicated below:

EUR 1.550,00 x 8 = EUR 12.400
Fee per additional invention number of additional inventions total amount of additional fees

Or, _____ x _____ = _____

The applicant is informed that, according to Rule 40.2(c), the payment of any additional fee may be made under protest, i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. ☒ Claim(s) Nos. see annex have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

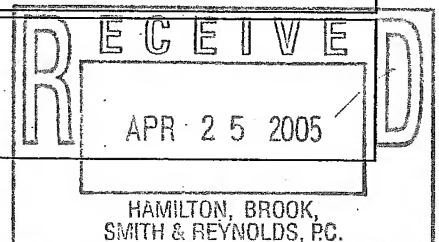
Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31.651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer:

Eva Boháčová



C179

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 950 417 A (PFIZER PRODUCTS INC) 20 October 1999 (1999-10-20) paragraphs '0031! - '0033!, '0036!, '0037!, '0066!, '0067!, '0113!, '0120! - '0122!; claims 4,10,15	1-5, 7-10,89
X	YAFFE A ET AL: "Combined local application of tetracycline and bisphosphonate reduces alveolar bone resorption in rats" JOURNAL OF PERIODONTOLOGY 01 JUL 2003 UNITED STATES, vol. 74, no. 7, 1 July 2003 (2003-07-01), pages 1038-1042, XP009044957 ISSN: 0022-3492 abstract	1-3
X	US 2003/207827 A1 (BOYLE WILLIAM J 'US! ET AL) 6 November 2003 (2003-11-06) paragraphs '0087! - '0108!	1-10,89
X	WO 99/45923 A (MERCK & CO., INC; FISHER, JOHN, E; RODAN, GIDEON, A) 16 September 1999 (1999-09-16) page 5, lines 24-30 page 20, lines 17-31	1-5, 7-10,89

-/--



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CRANDALL C: "Combination treatment of osteoporosis: A clinical review" JOURNAL OF WOMEN'S HEALTH AND GENDER-BASED MEDICINE 2002 UNITED STATES, vol. 11, no. 3, 2002, pages 211-224, XP009044958	89
X	ISSN: 1524-6094 page 216, right-hand column, paragraph 2 - page 220, right-hand column, paragraph 2; table 1	
X	----- EZRA A ET AL: "ADMINISTRATION ROUTES AND DELIVERY SYSTEMS OF BISPHOSPHONATES FOR THE TREATMENT OF BONE RESORPTION" ADVANCED DRUG DELIVERY REVIEWS, AMSTERDAM, NL, vol. 42, no. 3, 31 August 2000 (2000-08-31), pages 175-195, XP001056768 ISSN: 0169-409X page 190	1-5,9,10
A	----- NAKAMURA K ET AL: "Stimulation of endosteal bone formation by local intraosseous application of basic fibroblast growth factor in rats" REVUE DU RHUMATISME (ENGLISH EDITION) 1997 FRANCE, vol. 64, no. 2, 1997, pages 101-105, XP002320926 ISSN: 1169-8446 abstract	1-10,89
A	----- DESANTIS A ET AL: "Current and emerging therapies in osteoporosis" EXPERT OPINION ON PHARMACOTHERAPY 2002 UNITED KINGDOM, vol. 3, no. 7, 2002, pages 835-843, XP009044945 ISSN: 1465-6566 page 841, right-hand column, paragraph 2	1-10,89

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 206

Continuation of Box 3.

Claim(s) not searched:

-

Claims 1-10, 89: Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10, 89

Treatment of uncoupled resorbing bone (including osteoporotic bones) by administration of a bone forming agent and an anti-resorptive agent, wherein at least the former is locally administered into the bone.

2. claims: 11-20, 51-59, 80-88

Kit (for treating osteoporotic bone) comprising: an osteoconductive/bone growth material, an anti-resorptive agent, and means for delivering said agents into the bone

3. claims: 21-30

Method of treating osteoporosis in a patient by local administration of a highly specific cytokine antagonist into an uncoupled resorbing bone

4. claims: 31-49

Osmotic pump implant for providing sustained delivery of agent/s into a bone

5. claim: 50

Device for providing sustained delivery of an anti-resorptive agent into a bone with chamber, exit port and means for expelling the agent

6. claim: 60

Method of treating an osteoporotic patient by inserting a bone growth agent into a vertebral body, removing a portion of the intervertebral disc and inserting a spinal implant into the created disc space

7. claims: 61-69

kit (for treating osteoporosis) with a bone forming agent and a highly specific cytokine antagonist

8. claim: 70

Method of treating a non-tumorous uncoupled resorbing bone by locally administering an anti-resorptive agent into the bone

9. claims: 71-79

Drug delivery implant for providing sustained release of a therapeutic agent to a bone comprising a drug pump and a carrier

According to the description, the present International application provides compositions, formulations, methods and devices for treating osteoporosis. Said formulations, methods and devices have been grouped into 9 groups as defined above and have no technical features in common, except their intended use in administering 'a drug' to patients with osteoporosis/bone resorption problems. An priori lack of unity exists thus in the present case.

Even if the device claims are left aside, there is no common feature among the different therapeutic methods and compositions, since some claims refer only to anti-resorptive agents, some to bone growth agents and some to a combination of both.

All claims 1-10, 51-58, 61-69 and 80-80 have in common the combination of bone forming and anti-resorptive agents (The wording "for treating ..." in the kit claims is not considered to limit their scope, since the intended use does not change a product per se.) Said combination is well known in the art: see for instance: The New England Journal of Medicine, 25-09-2003, 349(13): 1207-1215, W099/45923 or W099/65482. Local treatment is also known (Journal of Periodontology, 01.07.2003; 74(7): 1038-42; or Advanced Drug Delivery Reviews, 31.08.2000; 42:175-195).

Hence, the claims with the combination of bone forming and anti-resorptive agents have been divided in:

- a) Method for treating bone resorption, characterized by local administration of at least the bone forming agent, (1-10, 89)
- b) kit with means for local delivery of at least the antiresorptive agent into the bone (sustained release device or bone anchor) (cl. 11-20, 51-59, 80-88),
- c) kit with a highly specific cytokine antagonist as anti-resorptive agent (61-69),

It is noted that the kit of claims 11-20 refers to osteoconductive agents. This term has been considered similar as "bone forming agents".

The set of claims contains thus several solutions to the general problem of providing formulations, methods and devices for treating bone resorption troubles/osteoporosis. Said different solutions do not share technical features which can be accepted as special technical features involved in the technical relationship among the different claims in the present application. As no other special technical features can be distinguished which could fulfil this requirement, there is no single inventive concept underlying the plurality of inventions of the present

application (see Rule 13.1 and 13.2 PCT).

Furthermore, it is noted that a search of inveniones 2 to 9 would have involved considerable extra search effort.

Patent Family Annex

Information on patent family members

International Application No

PCT/US2004/039589

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0950417	A	20-10-1999	BR 9900775 A	28-03-2000
			CA 2262269 A1	23-08-1999
			EP 0950417 A2	20-10-1999
			JP 11315030 A	16-11-1999
			US 6352970 B1	05-03-2002
			US 2002019351 A1	14-02-2002
US 2003207827	A1	06-11-2003	US 6369027 B1	09-04-2002
			US 6613544 B1	02-09-2003
			AU 710587 B2	23-09-1999
			AU 1468697 A	17-07-1997
			BG 63347 B1	31-10-2001
			BG 101813 A	30-09-1998
			CA 2210467 A1	03-07-1997
			CN 1182452 A	20-05-1998
			CZ 9702538 A3	17-03-1999
			DE 19654610 A1	26-06-1997
			EE 9700164 A	16-02-1998
			EP 0784093 A1	16-07-1997
			EP 0870023 A1	14-10-1998
			FR 2742767 A1	27-06-1997
			GB 2312899 A ,B	12-11-1997
			HU 9801122 A2	28-08-1998
			ID 17460 A	08-01-1998
			JP 11503616 T	30-03-1999
			NO 973699 A	21-10-1997
			NZ 326579 A	28-01-1999
			NZ 332915 A	28-07-2000
			PL 321938 A1	05-01-1998
			SK 110797 A3	12-07-1999
			TR 970550 A2	21-07-1997
			WO 9723614 A1	03-07-1997
			US 6284485 B1	04-09-2001
			US 6288032 B1	11-09-2001
			US 6284728 B1	04-09-2001
			US 6015938 A	18-01-2000
			US 6284740 B1	04-09-2001
			ZA 9610770 A	22-06-1998
WO 9945923	A	16-09-1999	AU 2901199 A	27-09-1999
			CA 2323448 A1	16-09-1999
			EP 1061917 A1	27-12-2000
			JP 2002506030 T	26-02-2002
			WO 9945923 A1	16-09-1999
			US 2001025028 A1	27-09-2001